Flow-mediated dilatation of brachial artery as marker of preeclampsia morbidity

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Dear Sir,

Despite the efforts that have been made, it is still difficult to predict preeclampsia and its morbidity [1]. Flow-mediated dilatation (FMD) is a technique that has been employed to investigate the role of vascular alterations in preeclampsia [2]. Our hypothesis is that FMD may be useful as a clinical test prognostic marker, specially associated with routine laboratorial exams. We therefore studied the association of endothelial dysfunction, assessed by FMD, with preeclampsia morbidity.

The study was approved by the Research Ethics Committee of Pontifícia Universidade Católica do Rio Grande do Sul (Protocol 368/11), and written consent was obtained from all participants before inclusion. This is a cohort study that enrolled women with preeclampsia at the diagnostic moment, accompanied until delivery. Women were grouped according to preeclampsia outcomes dividing into women with or without complications. Complicated preeclampsia was considered when any of the following occurred: HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), eclampsia, abruptio placentae, mother's Intensive Care Unit admission, maternal death, early prematurity (delivery before 34 weeks gestation), severe growth restriction (percentile < 5), newborn lighter than 2 kg, APGAR Score <7 in the fifth minute, need of Neonatal Intensive Care Unit admission or stillbirth. Twin pregnancy, women who were in labor on preeclampsia diagnosis and patients who withdraw consent were excluded.

Endothelial function was evaluated by brachial artery FMD, using the protocol adapted from Celermajer DS, et al. [3]. FMD was measured in the first day of diagnosis and all patients rested for 10 min before baseline evaluation. None smoked cigarettes or drank coffee for at least 8 h before the ultrasound exam. This protocol has previously been used in our hospital [4]. Ultrasounds were performed by two observers. Intraobserver variability was 6.2% and 6.8%. Intra-class coefficient was 0.91 between observers.

Sample size was calculated to detect a difference of one standard deviation in the FMD (90% power and alfa 0.05), estimating at least 22 subjects by group.

The study included 66 women with preeclampsia and two were excluded, one twin pregnancy and one that delivered in another city. The remaining 64 subjects were analyzed, 26 developed complicated preeclampsia and 38 had preeclampsia without associated morbidities. Clinical characteristics, laboratory and Doppler ultrasound values are summarized in Table 1.

FMD in complicated preeclampsia group was 7.44% (IQR 2.20–13.34%) while in preeclampsia group was 11.80% (IQR 5.36–16.66%) (P = 0.03) as shows Fig. 1a. To better evaluate FMD association with morbidity, a composite of major outcomes (HELLP syndrome, eclampsia or stillbirth) was selected from the complicated preeclampsia group and 13 women fit these criteria. FMD was 2.84% (IQR 0.00–7.22%) in this sub-group compared to 11.90% (IQR 5.56–16.62%) of all other women (P < 0,001) (Fig. 1b). At last, a cutoff value of FMD <4.5% was used for risk estimation [5]. It was associated with an *Odds Ratio* (OR) of 3.79 (IC 95% 1.23–11.70) for complicated preeclampsia and an OR of 15.55 (IC 95% 3.55–68.16) for predicting the composite major outcomes.

Endothelial dysfunction evaluated through FMD is known to be present in preeclampsia patients [2,4,6,7], but the association with severity of the disease has been poorly investigated. The present study demonstrates that decreased FMD may be linked directly to morbidity of preeclampsia. These results are in agreement with a study that evaluated preeclampsia and severe preeclampsia, showing worst endothelial function on the severe group, even though the authors haven't made a statistical comparison [2].

Endothelial dysfunction is thought to be one of the mechanisms involving preeclampsia manifestations (hypertension and proteinuria). While in normal pregnancy FMD increases throughout pregnancy [8], in women with preeclampsia it is reduced [6]. Also, FMD was altered even before the onset of the disease [2,7]. We tested its association with disease severity, supported by the theory of impaired nitric oxide bioavailability in preeclampsia [9,10]. Our results have shown that FMD

Table 1
Clinical characteristics, laboratory and Doppler exams.

	PE (n = 38)	Complicated PE (n = 26)	P
Age (years)[a]	27.5 ± 6.4	26.2 ± 7.1	0.41
Chronic hypertension n (%)[b]	10 (26.3)	10 (38.5)	0.29
Cigarette smoke n (%)[b]	4 (10.5)	6 (23.1)	0.49
Nulliparity n (%)[b]	16 (42.1)	13 (50.0)	0.61
SBP (mmHg) [a]	156 ± 17	167 ± 18	0.012
DBP (mmHg) [a]	98 ± 12	104 ± 13	0.045
GA diagnosis (weeks)[a]	35.6 ± 1.9	29.4 ± 4.4	<0.001
GA at term (weeks)[a]	37.5 ± 1.5	31.0 ± 4.4	<0.001
Birth weight (g)[a]	3.037 ± 546	1.482 ± 870	<0.001
P/C Ratio [c]	0.49 (0.27–0.71)	0.67 (0.36–4.67)	0.038
Proteinuria 24 h (mg) [c]	365 (295–474)	673 (471–2.614)	0.001
Uric Acid (mg/dL) [a]	4.5 ± 1.2	5.3 ± 1.4	0.013
AST (units/L)[c]	21 (17–26)	40 (24–109)	<0.001
ALT (units/L)[c]	19 (14–24)	36 (23–101)	<0.001
LDH (units/L)[c]	467 (405–558)	718 (546–1.190)	<0.001
Creatinine (mg/dL)[a]	0.71 ± 0.15	0.89 ± 0.28	0.02
Platelets (×1000/mcL)[a]	219 ± 65	169 ± 68	0.005
Uterine artery RI[a]	0.50 ± 0.10	0.68 ± 0.18	<0.001
Umbilical artery RI[a]	0.57 ± 0.08	0.70 ± 0.12	<0.001
Median cerebral artery RI[a]	0.81 ± 0.08	0.79 ± 0.07	0.47
FMD (%) [c]	11.80 (5.36–16.66)	7.44 (2.20–13.34)	0.034

GA-gestational age; AST-aspartate aminotransferase; ALT-alanine aminotransferase; LDH-lactate dehydrogenase; RI-resistance index; FMD-flow mediated dilatation; P/C ratio-proteinuria/creatininuria ratio; SBP-systolic blood pressure; DBP-diastolic blood pressure.

[a] Mean ± standard deviation and Student t test.
[b] Percentual and Qui-square test.
[c] Median (IQR 25–75) and Mann Whitney test.

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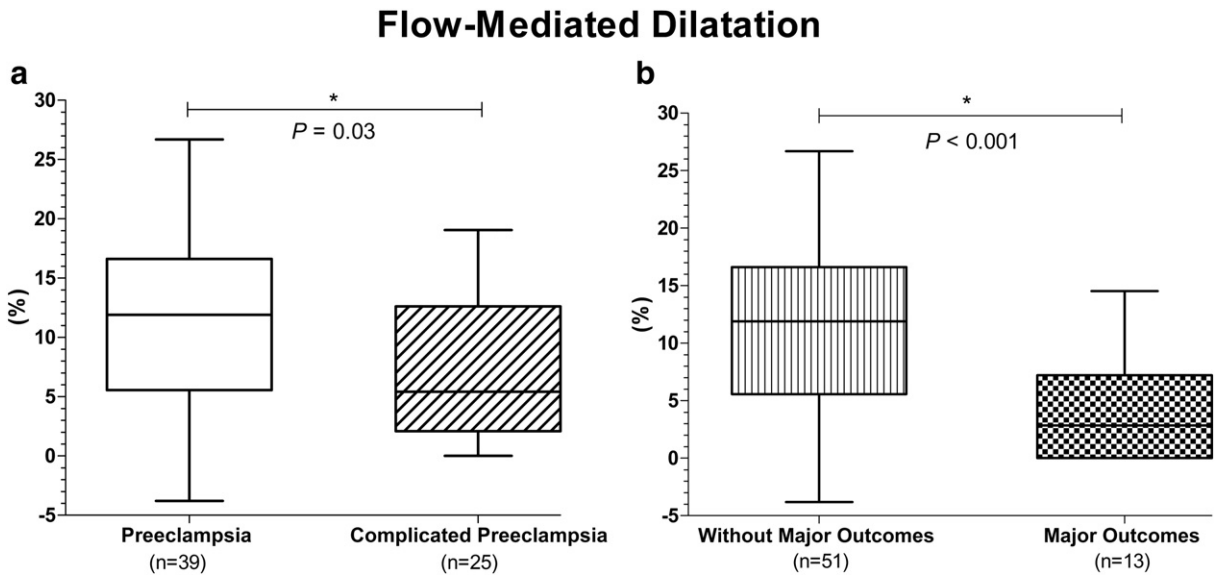

Fig. 1. Comparison of FMD between groups.

is impaired in complicated preeclampsia and it was reassured by the fact that in women with the worst outcomes it was remarkably lower. Furthermore, FMD of equal or less than 4.5% seems to be a reliable cutoff point associated with a four-fold increment of complications and a 15 fold increased risk of major outcomes. It is interesting to remember that low cutoff point should only be used in a set of patients with known impaired endothelial function [5], data is lacking to determine cutoff point for low risk population. Despite the fact that our study was not meant to determine prediction power, a preliminary analysis of the ROC curve suggests that FMD might be a weak prognostic marker for preeclampsia complications (AUC = 0.66; IC 95% 0.52–0.79). When used to predict major outcomes AUC increases markedly (AUC = 0.84; IC 95% 0.73–0.96).

Preeclampsia has many clinical presentations, it is a multisystemic disease that affects organs in different proportion, as illustrated by cases of preeclampsia without proteinuria or hypertension. FMD of brachial artery evaluates only one site, brachial artery endothelium, and sometimes it might not reflect the severity of whole disease. The variety of damage that can be caused by preeclampsia may be a limitation for this method to predict the disease and complications.

FMD of brachial artery is decreased in complicated preeclampsia in comparison with preeclampsia without complications. Severe endothelial dysfunction, measured by FMD test, is associated with higher risk of poor outcomes and may predict complications of the disease. Preeclampsia etiology and pathophysiology are not fully understood and probably this is the reason a specific predictor and prognostic marker haven't been found. Our findings support the evidence of endothelial dysfunction as a key mechanism for preeclampsia complications and also that FMD may be a prognostic marker.

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